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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
SCHMIDT, MARY M

ART UNIT	PAPER NUMBER
1635	20

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/301,380	Applicant(s) MURPHY ET AL.	
	Examiner Mary Schmidt	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,14,15,18 and 20-22* is/are pending in the application.

4a) Of the above claim(s) *2,14,15,18,20 and 21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-9 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 April 1999* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *18* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 2, 14-15, 18 and 20-21 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 15.

Specification

2. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s): the figures contain nucleic acid sequences which must be listed by SEQ ID NO: in the brief description of the drawings. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825) before the application can be examined under 35 U.S.C. §§ 131 and 132.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1, 3-9 and 22 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey

to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

MPEP 2163 teaches the following conditions for the analysis of the claimed invention at the time the invention was made in view of the teachings of the specification and level of skill in the art at the time the invention was made:

> **The claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence....A lack of written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process....Generally, there is an inverse correlation between the level of skill and knowledge in the art and the specificity of disclosure necessary to satisfy the written description requirement....The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice..., reduction to drawings..., or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.**

The claims as filed are drawn to administration of any Nr-Cam antisense to any species of whole organism. The specification teaches on page 123, Table 5, having antisense to human Nr-Cam. However, the antisense used in the murine studies was a full-length antisense expressed from a vector (see page 112). The claims as amended are drawn to antisense to human Nr-Cam

(SEQ ID NO:1) and no examples of use *in vivo* are taught in the specification as filed. Based on these teachings, of skill in the art would not have recognized that Applicant was in possession of a representative number of species of any Nr-Cam antisense as broadly claimed. See the 35 U.S.C. 112, scope of enablement rejection below, for references citing the unpredictability in the antisense art for design of a functional antisense to a target gene for use in cells *in vivo*. Applicant has not provided in the specification as filed the necessary sequence structure of other antisense which bind to Nr-Cam for the *in vivo* functions claimed. One of skill in the art would not have been able to readily visualize the sequences of Nr-Cam antisense which function *in vivo* absent further specific sequence structure design criteria. (As noted in the rejection below, antisense technology is dependant on finding complementary antisense sequence which will bind with high affinity to a particular location of the target gene sequence so that the affinity is high enough to function for the desired *in vivo* functions.) It is the nature of the antisense art that the structure and function of one antisense does not provide guidance to the structure and function of other antisense. Each antisense must be evaluated on an antisense-by-antisense basis. The specification as filed provides adequate written description for administration of murine full-length antisense to specific regions of mice taught by way of example in the specification as filed. However, such description does not teach how to design either antisense to human Nr-Cam, or how to design other Nr-Cam antisense for the claimed functions based on the instant disclosure. The description in the specification does not supplement the omitted description of

the specific sequence structure of other Nr-Cam antisense because specific, not general, guidance is what is needed.

Applicant is thus not considered to have been in possession of a representative number of species of antisense to human Nr-Cam commensurate to the breath of *in vivo* functions claimed.

5. Claims 1, 3-9 and 22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compositions comprising the specific antisense (claimed by SEQ ID NO.) to Nr-CAM of SEQ ID NO:1 taught in the specification as filed and methods of administration of the disclosed antisense *in vitro* (cells in cell culture) and via injection to the specific glioblastoma tumors taught by way of example in mice, does not reasonably provide enablement for any antisense molecule to Nr-CAM nor any method of use of such molecules in any whole organism for the methods of inhibition claimed *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claim 1 is drawn to a pharmaceutical composition for the inhibition of tumorigenesis comprising an antisense nucleic acid comprising at least 15 nucleotides hybridizible to at least a portion of an RNA transcript of a Nr-CAM gene of SEQ ID NO:1 in an amount effective to inhibit hyperproliferation of a tumor cell having high Nr-CAM expression. Claim 3 is drawn to a method of inhibiting cell overproliferation in a subject comprising administering to a tumor in a subject in which such treatment or prevention is desired an effective amount of Nr-CAM antisense nucleic acid comprising at least 15 nucleotides that inhibits Nr-CAM function, wherein

the Nr-CAM antisense nucleic acid is hybridizable to at least a portion of a RNA transcript of the Nr-CAM gene of SEQ ID NO:1. Claims 4-9 add the following limitations: (1) in which the disease or disorder is a malignancy; (2) in which the disease or disorder is selected from the group consisting of brain cancer, leukemia and B cell lymphoma; (3) in which the subject is a human; (4) in which the brain cancer is selected from the group consisting of glioblastoma, glioma, meningioma, astrocytoma, medulloblastoma, neuroectodermal cancer and neuroblastoma; (5) in which the glioblastoma is glioblastoma multiforme; (6) in which the disease or disorder is selected from the group consisting of premalignant conditions, benign tumors, hyperproliferative disorders, and benign dysproliferative disorders. New claim 22 specifies that the pharmaceutical composition of claim 1 comprises a liquid carrier.

The claims broadly read on administration of any antisense to inhibit Nr-CAM of SEQ ID NO:1 *in vivo* for the *in vivo* uses claimed. Note that the claims drawn to pharmaceutical compositions, have implied *in vivo* use. (This implication would be removed if the claims were amended to recite, a compositions comprising a pharmaceutically acceptable carrier, etc.)

The specification as filed teaches by way of example administration of pCMV1/3Nr-AS and pCMV1/3Nr-AS to mice glioblastomas and reduction of the tumor volume to no tumor. The specification as filed is enabling for administration of these antisense to glioblastomas by way of injection, but such results do not correlate to the breadth of the claimed invention for treatment of any tumor cell, by any means of administration with any molecule that inhibits Nr-CAM ligand encoding gene function.

The following is a restatement of the rejection made in the previous Official Action, with additional supporting references added:

There is a high level of unpredictability known in the antisense art for therapeutic, *in vivo* (whole organism) applications. The factors considered barriers to successful delivery of antisense delivery to the organism are: (1) penetration of the plasma membrane of the target cells to reach the target site in the cytoplasm or nucleus, (2) withstanding enzymatic degradation, and (3) the ability to find and bind the target site and simultaneously avoid non-specific binding (see Branch). Note also Ma et al. who teach (on page 167) that "to gain therapeutic advantage using antisense-based technology, ODNs must have certain characteristics. They must be resistant to degradation, internalize efficiently, hybridize in a sequence specific manner with the target nucleic acid, display adequate bioavailability with a favorable pharmacokinetic profile and be nontoxic." Despite the synthesis of more resilient, nuclease resistant, oligonucleotide backbones and isolated successes with antisense therapy *in vivo*, the majority of designed antisense molecules still face the challenge of successful entry and localization to the intended target and further such that antisense and other effects can routinely be obtained. Flanagan teaches, "oligonucleotides (*in vivo*) are not distributed and internalized equally among organs and tissues.... Unfortunantly, therapeutically important sites such as solid tumors contain very little oligonucleotide following intravenous injections in animals (page 51, column 2)." Ma et al. supports the difficulties of *in vivo* use of ODNs on pages 160-172. Jen et al. further taught that "given the state of the art, it is perhaps not surprising that effective and efficient clinical

translation of the antisense strategy has proven elusive. While a number of phase I/II trials employing ONs have been reported..., virtually all have been characterized by a lack of toxicity but only modest clinical effects." (Page 315, col. 2) Green et al. summarizes that "the future of nucleic acid therapeutics using antisense ODNs ultimately depends on overcoming the problems of potency, stability, and toxicity; the complexity of these tasks should now be apparent. Improvements in delivery systems and chemical modifications may lead to safer and more efficacious antisense compounds with improved pharmacokinetics and reduced toxicities." (P. 103, col. B) Note also some of the major outstanding questions that remain in the art taught by Agrawal et al. On page 79, col. 2.

In vitro, antisense specificity to its target may be manipulated by "raising the temperature or changing the ionic strength, manipulations that are commonly used to reduce background binding in nucleic acid hybridization experiments." (Branch, p. 48) Note also Ma et al. who teach that "*in vitro* subcellular distribution is dependent on the type of ODN modification, cellular system and experimental conditions. ODNs, once internalized, are distributed to a variety of subcellular compartments." (Page 168) Discovery of antisense molecules with "enhanced specificity" *in vivo* requires further experimentation for which no guidance is taught in the specification. Note Branch who teaches the state of the art for designing an antisense which inhibits a target *in vivo:* it "is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be found empirically by screening a large number of candidates for their ability to act inside cells (Branch, p.49)." Note Jen et al. who

teach that "although mRNA targeting is impeccable in theory, many additional considerations must be taken into account in applying these strategies in living cells including mRNA site selection, drug delivery and intracellular localization of the antisense agent." (Abstract) Bennett et al. further taught that "although the antisense paradigm holds great promise, the field is still in its early stages, and there are a number of key questions that need to be answered and technical hurdles that must be overcome....The key issues concerning this class of chemicals center on whether these compounds have acceptable properties as drugs. These include pharmacokinetic, pharmacological and toxicological properties." (Page 13) As argued above, these issues remain unpredictable in the art for antisense oligonucleotide administration *in vivo*.

The specification as filed teaches success of a locally administered, ie. injected, Nr-Cam antisense to a mouse, but such results are not predictive of (1) treatment effects via other routes of administration of said antisense, nor (2) correlation with whole organism success in other organisms such as human.

In regards to point (1) above, routes of administration of the antisense *in vivo*, the teaching of direct injection of an antisense does not correlate to other routes of administration to cells *in vivo*. As argued above, the antisense must be able to efficiently target the desired target gene location. Fritz et al. and Chirila et al. Teach common concerns in the design of suitable delivery vehicles for antisense oligonucleotides but teach the necessarily factors to be considered in the process. For instance Fritz et al. teach on page 272 that "[a]n efficient and versatile drug carrier system has to fulfill the following requirements: (I) particle sizes in the submicrometer

range; (ii) the possibility of surface modification; (iii) high drug loading capacity; (iv) colloidal stability of the latex in biological media; and (v) the lack of toxic side effects induced by the carrier or additives." Chirila et al. teach on mechanism of antisense action in vivo and the necessary requirement that the antisense be able to internalize into the desired cell target (see page 325). They teach on page 327 that "[e]ncapsulation or incorporation in liposomes is currently the preferred method for the delivery of AS ODNs... and, besides the intravenous infusion and subcutaneous, intramuscular or intraocular injection of naked ODNs, probably the only other method used in human clinical trials. (Ultimately, the suspensions of liposomes are also administered by infusion or injection.)." They also teach that the "in vivo delivery techniques chiefly used at the present, i.e. infusion or injection of naked molecules and liposomal systems, do not assure adequately long-term maintenance of ODNs in tissues." Without further guidance in the specification as filed for mechanisms for administration of the disclosed Nr-Cam antisense to other cancerous tissues in the desired subject, one skilled in the art would necessary practice "trial and error" experimentation to design and implement successful regimens for administration of the Nr-Cam antisense for the claimed functions. For instance, there is no guidance in the specification as filed as to how to avoid almost certain toxicity of administration of antisense to Nr-Cam (a gene expressed in many tissues *in vivo*) systemically.

In regards to point (2) above, correlation of murine and human treatment data, neither the specification nor the prior art taught how the administration of antisense to tumors in mice correlates to the actual administration of said antisense to other types of cancerous cells in other

whole organisms. Resor et al. taught a review on mouse modeling techniques useful for modeling human cancer. They teach in the specification that "transgenic approaches do no always completely and accurately model human carcinogenesis." They teach on page 669 that "[a]lthough these techniques have provided great insight, they do not fully model the vast majority of cases of cancer. In general, cancer arises because individual somatic cells sustain a series of sequential mutations that provide a growth or survival advantage, escape from senescence and the onset of genomic instability, thus perpetuating genetic changes that ultimately result in tumor formation. Standard transgenic and knockout techniques do not faithfully model such changes." The instant claims are drawn to inhibiting any cell proliferation in any individual *in vivo* comprising the administering to said individual a composition comprising a Nr-Cam antisense. The teachings of *ex vivo* administration of one type of cancer cell to mice followed by antisense delivery to the site, does not correlate to any other treatment effects of any cancer as broadly claimed in any whole organism. The teachings of Resor et al. summarize the lack of uniformity among the causes of different types of cancer, which preclude equivalent treatment of any such cancer in any individual. For another specific example of the lack of correlation between murine and human cancer pathology, Applicant is referred to the teachings of Blackshear. She taught on pages 105-106 that "[a]nimal models of spontaneous and chemically induced mammary gland carcinogenesis have provided some insight into the pathogenesis of breast cancer but do not faithfully mimic the pathology or biological behavior of human breast cancer.... there is no single model that best mimics the pathology and mechanistic deregulation

seen in breast cancer. Each model provides a small portion of the puzzle, which helps to clarify the complex interactions associated with eh heterogeneous population of cells in the normal mammary gland. These models enable the researcher to examine individual or combinations of perturbations that lead to the initiation and progression of breast cancer." Thus, absent use of an art recognized mouse model of human disease, the art teaches a high level of unpredictability for the correlation of specific treatment results in mice with an expectation of success of the equivalent effects in humans.

One of skill in the art would not accept on its face the successful delivery of any Nr-CAM antisense molecule *in vivo* and further, treatment effects, in view of the lack of guidance in the specification and the unpredictability in the art of the unpredictable factors argued above. Specifically the specification does not teach (1) stability of any Nr-CAM antisense molecules *in vivo*, (2)effective delivery to the whole organism and specificity to the target tissues by routes other than direct injection into the tumor, (3) dosage and toxicity of inhibitory molecules administered by any other route of administration than direct injection, nor (4) entry of molecule into cell and effective action therein marked by visualization of the desired treatment effects of any inhibitory molecule of Nr-CAM administered by any route of administration. These key factors are those found to be highly unpredictable in the art as discussed *supra*. The lack of guidance in the specification as filed for these factors would therefore require "trial and error" experimentation beyond which is taught by the specification as filed. Therefore, it would require undue experimentation to practice the invention as claimed.

Applicant's arguments filed June 5, 2002, have been fully considered but they are not persuasive.

Applicant responds on page 8 that "[o]n the contrary, the specification as filed provides a description of methods to produce antisense molecules other than the specific examples as well as methods for their administration to species other than mice and for the inhibition of various tumors having high Nr-Cam expression." However, the areas of the specification cited by applicant provide only prophetic uses of the claimed antisense and do not necessarily teach an expectation of success for any such antisense claimed *in vivo*. As argued above, there was a high level of unpredictability in the antisense art for design and administration of particular therapeutic antisense to whole organisms for treatment uses. New references were provided to support the unpredictability in the art and lack of guidance or expectation of success for correlating use of antisense that *in vitro* to use *in vivo*, correlating use of antisense in mice to use in human cancer treatments, and the further unpredictability in the use of liposomal carriers/pharmaceutical compositions of antisense *in vivo*.

Applicant argues that Flanagan as well as Ho and Hartwig taught use of antisense in treatment of cancer and other human diseases. However, as argued above, the success of an antisense *in vivo* must be determined on an antisense-by-antisense basis. The success of an antisense to one gene target, administered one way, to treat a particular set of disease conditions *in vivo*, does not correlate or provide substantial guidance for the design and use of antisense to other target genes, for administration to other types of cells for other treatment purposes.

Therefore, while Applicant argues that one of skill in the art would have been able to empirically determine how to design an antisense that hybridizes to a known target and manipulating the conditions *in vitro* to mimic *in vivo* cellular conditions, such ability in the art does not further provide substantial guidance on how to administer any such antisense to the desired cell targets *in vivo*, to overcome the unpredictable factors cited above (non-specific binding, entry to the desired target cells, lack of toxicity, sufficient concentration, etc.), or an expectation of success that one would be able to design an antisense that has the desired functions *in vivo*. The new references cited teach the lack of correlation between many cancer mice models and human cancer models, as well as the unpredictability in the use of liposomal carriers for the delivery of any desired therapeutic antisense. The fact that one of skill in the art could rationally design an antisense to a target such as Nr-Cam SEQ ID NO:1 in cells in culture, does not provide substantial guidance for use of any such antisense *in vivo* as claimed.

6. The claims are considered free of the prior art since the prior art did not teach antisense to Nr-Cam of SEQ ID NO:1 for the claimed *in vivo* uses in a subject for treatment or prevention of tumors.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *John LeGuyader*, may be reached at (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Analyst, *Kay Pinkney*, whose telephone number is (703) 305-3553.

M. M. Schmidt
August 26, 2002